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| 10/602,413 | 06/23/2003 | Denis Schrier | PCA391-D1-01-CFP | 9188 |

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| EXAMINER | |
|---|---|
| OLSON, ERIC | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1623 | |

DATE MAILED: 03/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/602,413 | SCHRIER ET AL. | |
| | Examiner | Art Unit | |
| | Eric S. Olson | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *June 23, 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,58 and 59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,58 and 59* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/23/03, 12/11/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## Non-Final Rejection

## Detailed Action

This application is a divisional application of 09/952787, now US patent 6620829, filed 10/17/2000. Claims 1-3, 58, and 59 are pending in this application and examined on the merits herein. Applicant's preliminary amendment submitted 6/23/2003 is acknowledged wherein claims 1, 2, 58, and 59 have been amended and claims 4-57 are cancelled.

## Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The disclosure is objected to because of the following informalities: the misspelled chemical name "ascetic acid" in a chemical name at the top of Example 40 on p. 188. The correct spelling is "acetic".

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Method of treating Noninflammatory Cartilage damage, in accordance with the revised title of the parent application. Please note that amendment to the claims in response to this office action may necessitate further

amendment to the title if the amended claims significantly decrease the scope of the invention so that the new title is no longer descriptive.

**Claim Objections**

Claim 2 is objected to because of the following informalities: The use of the phrase, "and pharmaceutically acceptable salts thereof". This phrase should read "or pharmaceutically acceptable salts thereof". Appropriate correction is required.

**Claim Rejections – 35 USC § 112**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 58 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 2, and 58 recite the phrase, "comprising administering a therapeutically effective amount of a GABA analogue" without stating to whom the GABA analogue is to be administered. A suggested revision is: "comprising administering to said mammal a therapeutically effective amount of a GABA analogue". Claims 3 and 59 are rejected for depending on the rejected claims 2 and 58, respectively.

Appropriate correction is required.

**Claim Rejections – 35 USC § 112**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating certain forms of cartilage damage in a mammal by administering a therapeutically acceptable dose of one of several GABA analogues of formula 1 disclosed in the specification as useful for treating cartilage damage in animal models, does not reasonably provide enablement for any compounds which could be described by the phrase "GABA analogue having the characteristic of being an inhibitor of cartilage damage". This is a purely functional distinction or functional language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to reliably determine the scope of the molecules claimed, absent undue experimentation.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The instant invention pertains to a method of using a GABA analogue as a therapeutic for the treatment of certain kinds of cartilage damage in a mammal. The method by which the compound is to be administered is expected to be similar for most GABA analogues, although certain functional groups, such as GABA analogues linked to phosphate groups or oligonucleotides, which are not excluded from a broad reading of the claim, may not be suitable for certain methods of administration, such as oral administration.

The state of the prior art: Cartilage is a multifaceted and incompletely understood tissue. While certain enzymes, such as matrix metalloproteases and nitric oxide synthase, are believed to play a role in the biochemical breakdown of cartilage, and thus in cartilage damage, no specific molecular target has been widely validated as a useful target for pharmaceutical treatments of cartilage damage. In fact, it is not shown in the prior art that there exists a single molecule, protein, gene, or biochemical pathway, which, if inhibited, activated, or otherwise modified by a pharmaceutical composition, would consistently prevent, block, or inhibit all types of cartilage damage. Thus a researcher seeking to determine the usefulness of a GABA analogue as a treatment for cartilage damage would be unable to draw on a well-defined prior art for guidance.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Note that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the

more specific enablement is necessary in order to satisfy the statute. In the case of osteoarthritis and other conditions of cartilage damage, the cause is incompletely understood and believed to be the result of a variety of different environmental, biomechanical, genetic, metabolic, and other factors, as stated by the Applicant's own disclosure (p. 1, lines 14-22). This level of unpredictability is further heightened by the lack of existing pharmaceutical treatments for cartilage damage with which proposed GABA analogs could be compared.

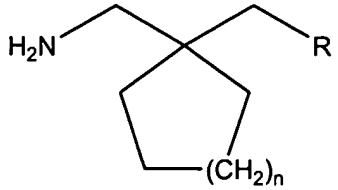
Thus, a skilled artisan would be unable to reliably predict the usefulness of a particular chemical compound for the treatment of cartilage damage in the absence of specific data demonstrating such usefulness for the same or closely related compounds.

The Breadth of the claims: Claim 1 recites the phrase "GABA analogue" to identify the pharmaceutical compound being used in the claimed method of treatment. To a skilled practitioner of the medical or pharmacological arts, this term indicates any organic compound derived from or based upon 3-gamma-amino-butyric acid. This broad class includes thousands of distinct molecules, all of which have some sort of similarity to GABA. Such compounds would include all of the compounds recited on pp. 4-29 of the specification, as well as many other classes of molecules, including but not limited to those related to 1-aminomethyl-2-carboxymethyl-benzene, and 3-amino-1-sulfonyl-propane, 3-aminocyclohexanoic acid.

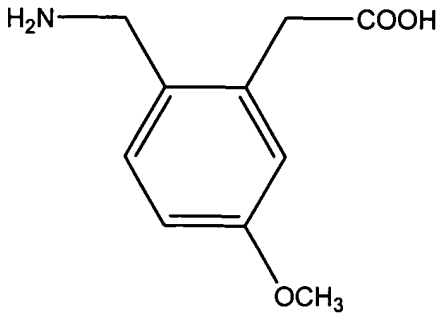
The amount of direction or guidance presented: The specification discloses two experimental protocols for testing the utility of a potential cartilage damage treating

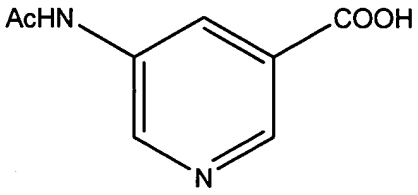
compound, disclosed on pp. 206-215 of the specification. Both protocols involve the administration of the compound to a live animal which is suffering from experimentally induced osteoarthritis. The specification also broadly suggests that, "A compound that is a GABA analog having the characteristic of being an inhibitor of cartilage damage may be readily identified by one of ordinary skill in the pharmaceutical or medical arts by assaying a GABA analog in any number of well known assays for measuring cartilage effects of a compound, and determining the GABA analog's effects on cartilage damage." (p. 29, lines 16-20) The specification further suggests several kinds of assays including both tissue cultures and whole animals. The specification does not disclose any general target or method of action by which the pharmaceutical molecules in the claimed invention exert their therapeutic effect, and against which potential drug candidates could be evaluated before performing the described experiments.

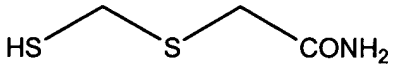
The presence or absence of working examples: The specification discloses several examples of GABA analogues which the inventors have determined to be useful in the claimed method of treatment. Tables disclosing these examples appear on pp. 209-210, 213, and 215 of the specification. In all, five distinct GABA analogues are disclosed as being useful for the treatment of cartilage damage and 3 which are not useful. With the exception of pregabalin, one of the non-active compounds, all of the compounds disclosed are of the formula:

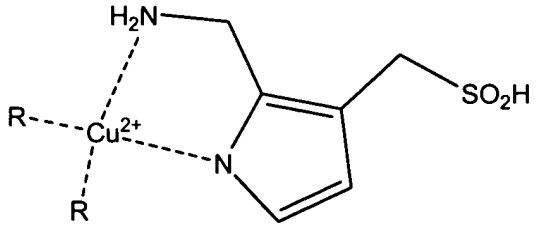


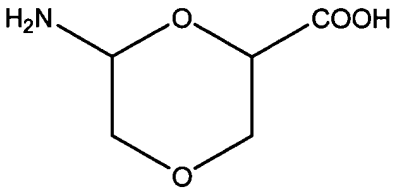
Where R = carboxylate or tetrazole or oxadiazole, and n = 1-3. These compounds represent a tiny fraction of the chemical space included in the term "GABA analog" and are not considered to be representative of most of the molecules claimed in claim 1. These examples would be of extremely limited use to one of ordinary skill in the pharmaceutical or medical arts in determining which GABA analogs are useful in the treatment of cartilage damage, and thus included in the scope of claim 1. For example, the following drug candidates:




Could all be reasonably called GABA analogues, yet none of them could reasonably be judged by analogy with the disclosed working examples.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the treatment of cartilage damage. See MPEP 2164.

The quantity of experimentation necessary: In view of the lack of any disclosure of the method by which the claimed invention exerts its effect, one of ordinary skill in the art wishing to practice the invention of claim 1 with the full range of GABA analogues beyond the meager number disclosed in the specification would be required to undertake *in vivo* tests in an animal model of cartilage damage such as the ones disclosed in the specification. Method A requires the use of at least 10 rabbits per compound tested for eight weeks. Method B requires the use of an undisclosed number of rats for 14 days. Animal experiments include, along with the actual administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Because of the unpredictability of the art and the lack of either comprehensive working examples or a general theory of GABA analog-induced cartilage protection in the specification, these animal experiments would need to be repeated hundreds of times, and involve the maintenance, killing, dissection, and disposal of thousands of experimental animals, to establish the activity or lack thereof of every possible GABA analog, presenting an undue amount of experimentation to anyone wishing to practice the invention.

*Genetech*, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the unpredictability of the art, the broad scope of the claim, the lack of direction or guidance as to the mechanism of action, the paucity of working examples, and the significant amount of necessary experimentation, Applicants fail to provide information sufficient to practice the claimed invention for the treatment of noninflammatory cartilage damage using any GABA analogue with the characteristic of being an inhibitor of cartilage damage.

**Claim Rejections – 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lu et. al. (Included in PTO-1449 submitted by Applicant) in view of Minor (Editorial in *Arthritis & Rheumatism* (1996) v.9 iss.2 pp79-81) and the entry for Osteoarthritis in the Merck Manual, seventeenth edition (pp.449-451).

Lu et. al. teach the use of gabapentin for the relief of nociceptive pain, including arthritic pain in particular. The data presented in figure 2, p. 217, demonstrate that administration of gabapentin to a rat suffering from experimentally induced arthritic pain reduces the severity of pain and hyperalgesia observed in the subject. The effect taught by this study is due to the relief of pain rather than the relief of inflammation, as

the extent of inflammation of the treated animal's paw was not observed to be any different from the control group. Lu et. al. do not teach the use of gabapentin for the treatment of noninflammatory cartilage damage in a mammal.

Minor teaches that regular exercise improves physical health, joint function, and muscle strength in patients suffering form osteoarthritis (OA). The Merck Manual (p. 451) teaches that, "Exercise (...) maintains healthy cartilage and range of motion and develops stress-absorbing tendons and muscles. Daily stretching exercises are of utmost importance. Immobilization for relatively short periods can accelerate or worsen the clinical course. Arrest and occasionally reversal of hip and knee OA can occur using well-planned exercise as therapy." It is also well known in the art that cartilage damage from OA can lead to pain which discourages patients from engaging in appropriate physical activity, leading to joint immobilization, muscle weakness, and weight gain, all of which accelerate the degeneration of the articular cartilage.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teaching of Lu et. al. by administering gabapentin to osteoarthritic patients who suffered from severe chronic pain which precluded them from engaging in a healthy level of physical activity. One would have been motivated to administer gabapentin to these patients both to improve their quality of life and to allow them to engage in therapeutic exercises and other physical activity which would partially prevent, block, or inhibit the course of the disease. One would have reasonably expected success in view of the well-established history of treating osteoarthritis with pain relieving medications. Although this line of reasoning does not involve a method of

treatment involving any direct inhibition of cartilage damage by gabapentin, it falls within the limits of the claimed invention. Specifically, the claims and specification fail to define the mechanism of action of the claimed method of treatment, or even to define that the claimed treatment must directly treat cartilage damage as opposed to indirectly treating it in the manner described. Accordingly, the invention taken as a whole is *prima facie* obvious.

**Claim Rejections – 35 USC § 101 Double Patenting**

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 58 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 4 of prior U.S. Patent No. 6620829. Claim 59 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 5 of prior U.S. Patent No. 6620829. This is a double patenting rejection.

**Conclusion**

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday through Friday, 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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3/15/06

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